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tetrahydro-1H,3H-oxpino[3',3':6,7]indolizino[1,2-b]quinolin-12-yl  
methyl]-4-methyl-hexahdropyridium chloride.--

~~Claims 5 to 9, cancel lines 1 and 2 of each and insert~~ --The

A<sub>3</sub> method of claim 18 wherein the compound is selected from the group  
consisting of--

REMARKS

The amendment is submitted to insert reference to the parent applications and to direct the claims to the method of use.

Applicants wish to call to the Examiner's attention the following three publications Hertzberg et al, J. Med. Chem. 1989, Vol. 32, page 715, (1982) page 718 as well as Wall et al, Cancer Res., Vol. 55, (1995), page 753 and Camptothecin; New Anti-Cancer Agents, Putmesil et al, (CRC Press, 1995), page 27. These references would lead one skilled in the art away from Applicants' invention which uses a 7-ring member  $\beta$ -hydroxy lactone for the treatment of cancer. For instance, in the Hertzberg et al reference in the second column page 718, it is stated "The inactivity of 10 reinforces the strict requirement for an  $\alpha$ -hydroxy lactone ring; clearly this region of the molecule is in very close contact with the enzyme-DNA complex."

The Wall et al reference in the first column of page 756 clearly teaches that the "Major reduction of anti-neoplastic

activity was noted as the result of reactions involving the hydroxy or lactone moiety in ring E. After acetylation of CPT, the resulting acetate (Compound 7) is virtually inactive. Other reactions also point to the absolute requirement of the  $\alpha$ -hydroxy group as shown by the fact that after replacement of this group by chlorine, both the resultant chloro analogue (Compound 8) and the corresponding reduction product, deoxycamptothecin (Compound 9) are inactive in L1210 leukemia. Reduction of the lactone under mild conditions to give the lactol (Compound 10) also results in complete loss of activity." The third reference teaches on page 27 "In summary, the  $\alpha$ -hydroxylactone in ring E was found to be an absolute requirement for in vitro and in vivo activity of CPT and its analogs." These references would clearly indicate to one skilled in the art that the 7-ring membered  $\beta$ -lactones would probably not have the activity since it was not related to the 6-membered ring of an  $\alpha$ -hydroxylactone. Therefore, it is believed that Applicants have clearly demonstrated the unexpected and patentable features of the claimed method.

It is deemed that Applicants have clearly demonstrated the patentable features of the present invention and favorable reconsideration of the application is requested.

Respectfully submitted,  
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